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Air Pollution, Temperature, and Regional Differences in Lung Cancer Mortality in Japan

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ABSTRACT. In this study, the authors investigated regional differences in lung cancer mortality in Japan, and, based on data acquired between 1970 and 1990 for 47 Japanese prefectures, estimated the relationship between regional lung cancer mortality and air pollution and/or temperature. Investigators used data for nitrogen dioxide, sulfur dioxide, motor vehicle density, tobacco expenditure, and temperature as independent variables for age-adjusted lung cancer death rates. The age-adjusted lung cancer death rates were higher in the southern geographical block of Japan (i.e., approximately 1.2-fold in males and 1.1-fold in females) and in the northern block (approximately 1.2-fold in males) than in the central block. The regional differences in the age-adjusted lung cancer death rates were explained by nitrogen dioxide and temperature. Temperature caused a greater effect (regression coefficients) of nitrogen dioxide on the age-adjusted lung cancer death rates than did nitrogen dioxide alone in the southern block (i.e., approximately 1.3-fold in males and 1.2-fold in females). These results provide the first evidence of a possible synergistic interaction between air pollution and high temperature on lung cancer mortality.

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LUNG CANCER MORTALITY has increased continuously in Japan. Standardized death rates in Japan were 45.3 in males and 11.9 in females per 100 000 population in 1991; these rates were 3.3-fold and 2.5-fold, respectively, more than rates for 1960.[1] Doll[2] reported a relationship between lung cancer and cigarette smoking in 1950; many subsequent epidemiological studies have been conducted by investigators who have confirmed Doll's finding.[3-7] Cigarette smoking, therefore, is regarded as the main cause of lung cancer, and air pollution from vehicular traffic may also be a cause of lung cancer in urban areas.[8] In Japan, high lung cancer mortality is found in areas along the coast and in industrialized districts.[9] These regional distributions likely result in part from geographic differences in levels of air pollution, including photochemical air pollutants. High levels of nitrogen dioxide (NO_2)—the major oxidant air pollutant in urban atmosphere—adversely affects the human respiratory tract[10,11] and also promotes the development of lung tumors initiated by carcinogens in mouse lungs.[12-14] The association between levels of NO_2 and lung cancer mortality has not, however, been well established in communities. Katsouyanni et al.[15] reported that air pollution was associated with increased mortality and that the mean daily number of deaths increased when the air temperature exceeded 30 °C. These associations suggest that global warming and climate changes may increase the adverse effects of air pollution on health, thus causing new environmental health problems. The increase in NO_2 in urban areas is related closely to the increase in air temperature[16]; in the central region of the urban area, temperature is in-

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verted by subsidence heating, and this leads to excessive levels of air pollutants.[17] The results of in vitro experiments have showed that absorption of pollutants increases temperature dependently,[18,19] thus suggesting an interaction between temperature and metabolism of carcinogens. However, epidemiological studies on the association between lung cancer and air pollution and temperature in the general population have not been reported.

We investigated the geographic distribution of lung cancer mortality in Japan and estimated the relationship between regional lung cancer mortality and air pollution and/or temperature. We based our study on data gleaned for the 47 Japanese prefectures between 1970 and 1990.

Material and Method

Data on lung cancer deaths. We used official data of the Statistics Bureau Management and Coordination Agency, Japan, to obtain the lung cancer death rates for each of 5 calendar years: 1970, 1975, 1980, 1985, and 1990. Given that lung cancer mortality tends to be influenced by the age structure of the population, we used the direct method and the Japanese 1980 standard population to adjust, for age, lung cancer death rates for each of the 47 prefectures. We used these age-adjusted lung cancer death rates (ADRs) per 100 000 population) in all statistical analyses.

Environmental data. We chose five environmental factors—NO_2, sulfur dioxide (SO_2), motor vehicle density, air temperature, and tobacco expenditure—to investigate whether these factors were related to regional differences in ADRs. We obtained all data from published official data for each of the years given in the previous section. Data on air pollution in 1970 were not totally available because monitoring stations were not established all over the country. We used data on NO_2 and SO_2—obtained from published reports of the Environment Agency, Japan—to calculate the annual air pollution levels of total areas and residential areas measured at about 1 600 pollution-monitoring sites throughout Japan. We counted the number of monitoring sites at which the yearly mean of NO_2 and SO_2 exceeded 20 ppb (i.e., World Health Organization guideline for SO_2) to reflect more accurately the air pollution levels to which inhabitants would be exposed. We also used motor vehicle data because much of NO_2 comes from automobile exhaust in urban areas and because diesel-powered vehicle exhaust is a recognized carcinogen.[20] We calculated motor vehicle densities as the number of motor vehicles (i.e., registered motor vehicles, including buses, trucks, and passenger cars) per area of residential land (i.e., km^2) of each prefecture.

We compiled annual levels of mean and maximum monthly temperatures from monthly reports published by the Japan Meteorological Agency, and we counted the number of days during which the maximum daily temperature exceeded 30 °C for each prefecture. We calculated the annual average temperature as an arithmetic mean. Data on prefectural cigarette consumption were not available in any published report; therefore, we used tobacco expenditures as indirect indices of cigarette consumption. Tobacco expenditure is the tobacco tax per adult population in each prefecture. Particulate air pollution, especially fine particulates, may also be a potent cause of lung cancer.[21–23] In this study, however, we did not analyze data of the particulates because, until the late 1980s, monitoring stations had not been established throughout the country.

Statistical analyses. Geographic distributions of the ADRs were differentiated initially. We evaluated multiple simultaneous comparisons among blocks by the method of Scheffé.[24] We calculated simple correlations separately to describe the relationship between the ADRs and each independent variable. There may have been a time lag of more than 10 y between environmental exposure and ADRs; therefore, we analyzed correlations not only between annual average ADRs in 1970–1990 and the annual average levels of environmental factors in 1970–1990, but we also analyzed correlations between the ADRs in 1990 and the levels of environmental factors in each of the years 1970, 1970–1980, and 1970–1990. We used multiple regression analyses to evaluate the relative contribution of environmental factors to the ADRs and the combined effects of pollutants and temperature on the regional differences in ADRs. We entered independent variables in backward stepwise procedures, and these procedures were stopped when a statistical significance of the independent variables entering the regressions was less than .05. After selecting the significant multiple regressions, we estimated the magnitude of regression coefficients.

Definitions of blocks. We divided the 47 prefectures into three broad blocks: block 1, northern block: Hokkaido and Tohoku districts, including 7 prefectures; block 2, central block: Kanto and Chubu districts, including 16 prefectures; block 3, southern block: Kinki, Chugoku, Shikoku, and Kyushu districts, including the remaining 24 prefectures.

Results

Regional differences in ADRs. Generally, ADRs in the southern and northern blocks were higher than those in the central block (Fig. 1). In 1970, the mean ADRs in blocks 1, 2, and 3 were 22.6, 20.2, and 22.4 in 100 000 males, respectively, and 7.0, 6.7, and 6.9 in 100 000 females, respectively; in 1990, the respective mean ADRs had risen to 46.5, 40.2, and 45.6 in 100 000 males and to 10.9, 10.1, and 11.6 in 100 000 females (Table 1). We observed significant differences in the ADRs between the three blocks in 1990 and in 1970–1990; the differences were especially more apparent in males ($p < .001$) than in females ($p < .05$). Compared with the ADRs in block 2, the ADRs in block 3 were significantly higher in both males and females ($p < .01$ and $p < .05$, respectively), and the ADRs in block 1 were higher only in males ($p < .05$), we did not observe significant differences between blocks 1 and 3 in any time period.

Regional differences in environmental factors. The annual NO_2 levels of total areas in blocks 1, 2, and 3

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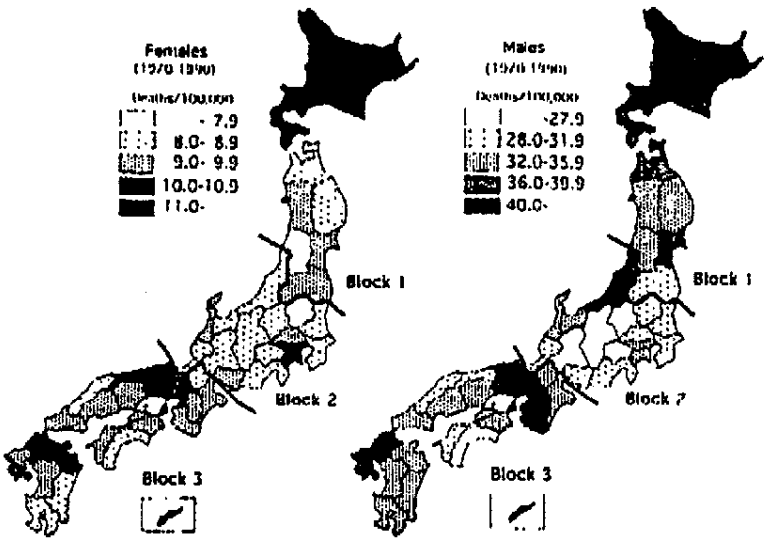

Fig. 1. Geographic distribution of age-adjusted lung cancer death rates (ADRs), by sex and prefecture. Forty-seven Japanese prefectures were grouped into three broad blocks: block 1, northern block—7 prefectures; block 2, central block—16 prefectures; block 3, southern block—24 prefectures.

Table 1.—Comparison of Age-Adjusted Lung Cancer Death Rates between Three Geographical Blocks, by Period and Sex

	Age-adjusted lung cancer mortality (per 100 000)						
	Block 1		Block 2		Block 3		
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	*p*
1970							
Males	22.6	2.9 A	20.2	3.3 A	22.4	2.9 A	NS
Females	7.0	1.4 A	6.7	1.1 A	6.9	1.6 A	NS
1990							
Males	46.5	3.3 A	40.2	4.5 B	45.6	4.8 A	< .001
Females	10.9	1.5*	10.1	1.5 A	11.6	1.7 B	< .05
1970–1990							
Males	35.4	2.7 A	30.5	3.3 B	35.1	4.0 A	< .001
Females	9.1	1.0*	8.8	0.9 A	9.6	1.1 B	< .05

Notes: A and B indicate significant differences between blocks (a repeated letter means no significant difference [NSI]). $\bar{x}$ = mean, and *SD* = standard deviation.
*No significant differences from the other two blocks.

were 10.1 ± 2.1 ppb (mean ± standard deviation), 17.0 ± 5.9 ppb, and 13.0 ± 5.0 ppb, respectively, and we observed significant differences between blocks 1 and 2 ($p < .05$) (Table 2). The annual SO_2 levels of total areas in blocks 1, 2, and 3 were 7.1 ± 1.4 ppb, 9.1 ± 1.9 ppb, and 8.9 ± 1.6 ppb, respectively; significant differences existed between blocks 1 and 2 and between blocks 1 and 3 ($p < .05$). The proportions of monitoring sites where yearly means exceeded 20 ppb for NO_2 in blocks 1, 2, and 3 were 2.7 ± 3.3%, 30.7 ± 33.1%, and 15.5 ± 20.1%, respectively; those for SO_2 were 2.5 ± 2.5%, 5.5 ± 4.8%, and 4.3 ± 4.8%, respectively. We observed significant differences between blocks 1 and 2 for NO_2, but not for SO_2. The levels of NO_2 and SO_2 in residential areas were similar to those for the total areas. During the study periods, the annual mean level of NO_2 remained almost constant in all three blocks, but that of SO_2 steadily declined annually. Motor vehicle density (vehicles per resident land/km²) in blocks 1, 2, and 3 were 2 622 ± 204, 3 463 ± 978, and 3 498 ± 703, respectively; we observed significant differences between blocks 1 and 3 ($p < .05$). The annual mean temperatures and number of days (per year) during which the maximum daily temperatures exceeded 30 °C in all blocks were 10.9 ± 1.5 °C, 14.3 ± 1.2 °C, and 16.1 ± 1.6 °C and 24 ± 13 d, 44 ± 13 d, and 60 ± 12 d, respectively.

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Table 2.—Comparison of Levels of Environmental Factors between Three Geographical Blocks, 1970–1990

Environmental factors	Block 1 $\bar{x}$	Block 1 *SD*	Block 2 $\bar{x}$	Block 2 *SD*	Block 3 $\bar{x}$	Block 3 *SD*	*p*
Nitrogen dioxide							
Total areas (ppb)	10.1	2.1 A	17.0	5.9 B	13.0	5.0†	< .01
Resident areas (ppb)	9.2	2.9 A	17.0	5.5 B	13.1	5.3†	< .01
Rate of sites ≥ yearly mean of 20 ppb (%)*	3.7	3.3 A	30.7	33.1 B	15.5	20.1†	< .05
Sulfur dioxide							
Total areas (ppb)	7.1	1.4 A	9.1	1.9 B	8.9	1.6 B	< .05
Resident areas (ppb)	7.0	1.6 A	8.9	1.6 A	8.5	2.2 A	NS
Rate of sites ≥ yearly mean of 20 ppb (%)*	2.5	2.5 A	5.5	4.8 A	4.3	4.8 A	NS
Motor vehicle density‡	2 622	204 A	3 463	978†	3 498	703 B	< .05
Temperature							
Arithmetric mean (°C)	10.9	1.5 A	14.3	1.2 B	16.1	1.6 C	< .0001
Mean of monthly max. (°C)	15.4	1.6 A	18.9	1.1 B	20.4	1.4 C	< .0001
No. of days/y ≥ 30 °C	24.0	11.0 A	44.0	13.0 B	60.0	12.0 C	< .0001
Tobacco expenditure (¥)§	2 574	362 A	2 724	285 A	2 529	266 A	NS

Notes: A, B, and C indicate significant differences between blocks (a repeated letter means no significant difference [NS]). $\bar{x}$ = mean, and *SD* = standard deviation.
*Computed as no. of sites ≥ 20 ppb/total sites.
†No significant differences from the other two blocks.
‡Vehicles/resident land - km².
§Total tax per adult per year.

Table 3.—Pearson Correlation Coefficients between Age-Adjusted Lung Cancer Death Rates and Environmental Factors in 1970–1990, by Sex and Geographical Block

Environmental factors	ADRs in males: Block 1 (*n* = 7)	ADRs in males: Block 2 (*n* = 16)	ADRs in males: Block 3 (*n* = 24)	ADRs in females: Block 1 (*n* = 7)	ADRs in females: Block 2 (*n* = 16)	ADRs in females: Block 3 (*n* = 24)
Nitrogen dioxide	.028	.043	.377	.287	.738*	.476†
Sulfur dioxide	−.124	−.182	−.122	.407	.596†	−.012
Motor vehicle	.038	.269	.366	.267	.867*	.458†
Temperature	−.472	.207	.514*	−.418	.485	.352
Tobacco tax	.156	.244	.671*	.760†	.682*	.630*

*$p < .01$.
†$p < .05$.

There were apparent significant differences between the three blocks ($p < .001$). Temperatures increased steadily from 1970 to 1990, except during the year 1980. The annual mean temperatures in blocks 1, 2, and 3 rose 1.9 °C, 1.9 °C, and 1.6 °C, respectively, in 1990 from those in 1970. Tobacco expenditures (in yen per adult/y) in blocks 1, 2, and 3 were ¥ 2 574 ± 362, ¥ 2 724 ± 285, and ¥ 2 529 ± 266, respectively; we did not observe any significant regional differences.

Simple correlations between ADRs and environmental factors. The correlations between average ADRs and annual average levels of each independent variable during 1970–1990 are shown in Table 3. Female ADRs in block 2 correlated with NO_2 ($r = .738$, $p < .01$), SO_2 ($r = .596$, $p < .05$), motor vehicle density ($r = .867$, $p < .01$), and tobacco tax ($r = .682$, $p < .01$); in block 3, female ADRs correlated with NO_2 ($r = .476$, $p < .05$), motor vehicle density ($r = .458$, $p < .05$), and tobacco tax ($r = .630$, $p < .01$). Male ADRs correlated with temperature and tobacco tax only in block 3 ($r = .514$ and 0.671, respectively; $p < .01$). We observed similar correlations between the ADRs in 1990 and the levels of environmental factors in each of the years 1970, 1970–1980, and 1970–1990 (data not shown). The levels of NO_2 and ADRs in the 47 prefectures and 3 blocks are shown in Figure 2. Although levels of NO_2 were lower than in block 2, general ADRs were higher in each prefecture in block 3 than in block 2. These results cannot be explained by a single factor (e.g., increase in air pollutants).

Relationships between ADRs and pollutants or temperatures. We conducted multiple regression analyses to explain the relative contribution of each independent variable to the ADRs and to estimate the effects of combinations of environmental factors on the regional differences in ADRs. Given that regional significant differ-

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Table 7.—Results of Multiple Regression Analysis for Association between Age-Adjusted Lung Cancer Death Rates and a Combination of Nitrogen Dioxide and Temperature in Females

Variables	Block 1		Block 2		Block 3	
	Regression coefficient	t	Regression coefficient	t	Regression coefficient	t
Nitrogen dioxide	0.114	0.621	0.115	0.010	0.119	0.003
Temperature	-0.272	0.431	0.029	0.885	0.304	0.012
Intercept	10.966	0.062	6.422	0.020	3.205	0.113
R^2	0.230		0.546		0.429	
F	0.597		7.821*		7.887*	

*$p < .01$.

Table 8.—Estimation of Regression Coefficients of Nitrogen Dioxide (NO_2) for ADRs When a Combination of NO_2 and Temperature is Associated with ADRs, by Sex and Geographical Block

	Block		
	1	2	3
Males			
NO_2	0.036	0.025	0.300
NO_2 + temperature	-0.045	-0.082	0.391*
Females			
NO_2	0.139	0.118*	0.101†
NO_2 + temperature	0.114	0.115†	0.119†

*Regression coefficients of NO_2 are significant at $p < .01$.
†Regression coefficients of NO_2 are significant at $p < .05$.

serve a significant difference in the pollutant levels between blocks 2 and 3.

In our survey, we found differences in many aspects related to ADRs between males and females. First, we observed significant correlations for both blocks 2 and 3 between female ADRs and levels of NO_2 and motor vehicle density. These correlations, however, were not observed in males; perhaps other factors (e.g., smoking, occupation) in males masked the effects of air pollutants on the ADRs. Second, in each block female ADRs also correlated with tobacco tax, but male ADRs correlated in block 3 only. There are possible explanations for the different correlations between females and males: (a) in each block, identical influences of tobacco for ADRs existed (at least for females); and (b) females—more than males—reflected environmental factors to which the population would be exposed. Finally, ADRs were approximately 3.7-fold as frequent in males as in females; perhaps this result, which has also been reported elsewhere,[40,41] evolved from a complex exposure in males.

Adverse health effects caused by air pollution are related to high temperatures,[42] as well as to low temperatures.[43] Photochemical air pollutants (e.g., NO_2 and ozone) are derived from photochemical reactions in the atmosphere associated with solar ultraviolet radiation[10] and temperature.[44] Investigators have also suggested in recent reviews that a possible biological synergy exists between air pollution and high temperatures and adverse effects on health.[45] Thus, the relationship between lung cancer mortality and NO_2 or temperature is plausible, but it has not been reported.

In this study, ADRs were not associated with temperature only. Although NO_2 levels, which corresponded with regional variations in female ADRs in both blocks 2 and 3, were slightly lower in block 3 than in block 2, the general ADRs in each prefecture in block 3 were higher than those in block 2 (Fig. 2). These results suggest that an increase in ADRs is likely to depend upon a combination of environmental factors, including air pollution and temperature. In the multiple stepwise procedure, the best relationships were observed between the ADRs and the combination of NO_2 and temperature for both males and females (significant in block 3 only). This obviously resulted from the intercorrelations between NO_2 and high temperatures, and this suggests a combined effect of these two variables on ADRs. Levels of ADRs in block 1 were similar to those in block 3, although levels of air pollutants in block 1 were the lowest.

The potential influence of pollutants on ADRs can be explained by the regression coefficients. When we combined NO_2 and temperature, the regression coefficients of NO_2 for ADRs were larger than those for NO_2 alone; however, these were significant only in block 3 (Table 8). These results suggest that high temperatures enhanced the effect of NO_2 on lung cancer.

In this study, we examined the association of regional lung cancer mortality with relatively low levels of air pollution in three different temperature blocks. Japan was appropriate for this purpose because temperature in Japan varies considerably between northern and southern geographical locations. We can explain regional differences in ADRs by NO_2 and temperature. Although the air pollution levels in block 1 (i.e., northern block) were lowest and were not correlated with ADRs in the block, levels of ADRs were similar to those in block 3 (i.e., southern block). This indicated that unknown environmental factors related to low temperature (e.g., air pollutants derived from heating) may have

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affected ADRs in the northern block. We note, however, that the ADRs in block 3 were significantly higher than in block 2 (central block); differences in the pollutant levels between blocks 2 and 3, however, were not significant. This finding suggests that effects of NO_2 on ADRs increased as the temperature increased. Actually, the annual mean temperature in block 3 was significantly higher (i.e., approximately 1.13-fold) than that in block 2.

In conclusion, air pollution, especially NO_2, was associated with lung cancer mortality in females, and exposure to both air pollution and high temperature induced an increase in lung cancer mortality in the general population. In the estimation of relationships between air pollution in atmosphere and lung cancer in the community, we need further epidemiological surveys to define individual exposure to air pollution; we must also explain adequately problem factors (e.g., smoking, occupation). Nevertheless, we believe that our study was useful because we demonstrated the combined effects of NO_2 and high temperatures on lung cancer mortality by multiple regression. We also provided evidence, for the first time, of a possible synergistic interaction between air pollution and high temperature with respect to lung cancer.

Finally, cigarette consumption in many countries has declined steadily; this has likely resulted from the worldwide effort to ban smoking. A decrease in lung cancer mortality is expected.[46] More and more cities, however, are facing the problem of increased urban air pollution (e.g., NO_2, CO_2), which is also linked to global warming. In this study, we demonstrated the influence of the combination of NO_2 and temperature on ADRs. Once smoking is banned, air pollution and temperature as risk factors of lung cancer will attract the attention of investigators. Further epidemiological or experimental studies are needed in which investigators explore the mechanism(s) of our evidence in light of future increases in air pollution and changes in climate.

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